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REVIEW ARTICLE

Basic and clinical insights of Mu (μ)-opioid receptor in cancer

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Abstract

Cancer is a public health problem that is extremely harmful to people's health. Most cancer patients experience severe pain in the advanced stage, which will seriously affect their prognosis. At present, opioids, such as morphine, have been used as the drug of choice for treating moderate to severe cancer-related pain. Mu (μ)-opioid receptor (MOR) is expressed in many different cancer cells. In this article, we present the relationship between MOR and tumor pathophysiology; summarize the molecular mechanism and effect of MOR on tumor proliferation and progression, tumor angiogenesis, tumor immunity, and cancer therapy; and propose the future research direction of MOR for cancer treatment. MOR could be as a promising prognostic biomarker and immune checkpoint in cancer therapy.

Keywords: Opioids; Mu-opioid receptor; Cancer; Angiogenesis; Immunotherapy

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1. Introduction

Cancer is one of the biggest public health problems in the world that endangers human health. In 2020, the number of cancer cases worldwide was 19,292,789, and the number of deaths was 9,958,133, according to the Global Cancer Observatory (GLOBOCAN)[1,2]. Among the different types of cancer, lung cancer, colorectal cancer (CRC), stomach cancer, liver cancer (LC), and breast cancer (BC) have the highest detection rates[3]. However, the methods used in cancer treatment, such as surgery, chemotherapy, and radiotherapy, have not been able to completely cure the tumor. Therefore, it is an urgent matter for researchers to explore efficient methods that can be used to treat cancer. This requires a comprehensive understanding of the pathophysiological process of tumor occurrence and development *in vivo*. The imbalance of epigenetic mechanisms is thought to play a key role in the occurrence and development of tumors[4,5]. In addition to the epigenetic imbalance of classic proto-oncogenes and tumor suppressor genes, there is new evidence that tissue-specific genes may also be targets for cancer epigenetic disorders[6-9]. The balance between pro-angiogenic factors and anti-angiogenic factors has a significant impact on tumorigenesis[10,11].

In the pathophysiology of tumor, cancer cells from the primary tumor will spread to distal tissues and form new tumor colonies, and it is a well-known fact that cancer metastasis has become the main reason for the high mortality rate of cancer[12,13]. Cancer metastasis involves a variety of cellular mechanisms, including local invasion of cancer cells in the primary tumor, entry into the tumor vasculature, stagnation in distal capillaries, extravasation into the parenchyma of target organs for metastatic colonization, evasion of immune surveillance, and regulation of tissue microenvironment[14-17]. Recently, clinicians have found that opioids and mu (μ)-opioid receptor (MOR) could affect tumorigenesis and tumor development when used to treat acute and chronic pain in cancer patients[18,19].

2. Mu-opioid receptor and its functions

Opioids are a class of alkaloids extracted from the opium poppy, including morphine, codeine, *etc*. Opioids have long been considered one of the most effective drugs for treating pain, including acute severe pain and chronic pain[20-22]. In 1975, Hughes *et al*.[23] discovered two endogenous biopeptides with potent opioid activity in the human brain. Opioids and endogenous opioid peptides work by binding to specific protein receptors (opioid receptors).

Opioid receptors are mainly distributed in the central and peripheral nervous systems[24], and their activation could produce peripherally or both peripherally and centrally mediated effects, such as decreased visceral smooth muscle peristalsis, pupil narrowing, lethargy, clouding of consciousness, and respiratory depression[25-28]. Opioids in the central nervous system (CNS) could lead to changes associated with hyperalgesia and sensitization[29-31]. Moreover, the activation of the opioid system in other CNS pathways may modulate emotions, including irritability and euphoria[32,33].

The opioid receptor is a G protein-coupled receptor (GPCR) located in the cell membrane, cytoplasm, or nucleus and is one of the most abundant class of cell membrane surface receptors[34]. This receptor is an important drug target for pain management, addiction, and emotion regulation, including MOR, kappa (κ)-opioid receptor (KOR), delta (δ)-opioid receptor (DOR), and nociceptive peptide opioid receptor, each of which is divided into several subtypes[35,36]. MOR, KOR, and DOR are widely distributed in the brain, brainstem downlink pathways, and dorsal horn of the spinal cord in the CNS and are present peripherally in the heart, digestive tract, and immune system[37-40]. Endogenous pain-sensitive peptides, the fourth member of the opioid receptor family, are known as opioid receptor-like 1 (ORL1), which have been successfully isolated by Mollereau *et al*.[41,42].

2.1. Mu-opioid receptor

MOR can be divided into three subtypes (MOR1, MOR2, and MOR3) and activated by a variety of synthetic compounds, such as morphine, and endogenous opioid ligands, including endorphins, enkephalins, and dynorphins[43,44]. MOR is widely distributed in the central and peripheral nervous systems, and it affects the physiological function of neurons when activated, thereby producing both analgesic effects and adverse effects, such as respiratory depression, nausea, vomiting, constipation, and addiction[45-47]. Moreover, it can inhibit the occurrence of immune and inflammatory responses, which are associated with tumor vascular endothelial cell proliferation[48]. MOR is also expressed in other cells, such as lymphocytes, macrophages, pancreatic endocrine cells, and gastrointestinal secretory cells, where it could regulate inflammation, glucose metabolism, and gastrointestinal motility (Figure 1)[48-50].

MOR exhibits bidirectional effects during tumorigenesis and tumor development[51], and many studies have shown that opioids induce tumor angiogenesis and tumor cell growth by stimulating the MOR, thus promoting metastasis[52,53]. However, there are studies that have suggested that MOR induces an opposite effect in other cancer cells. MOR overexpression has shown to promote tumor growth and metastasis in human liver cancer and laryngeal cancer[54,55]. The expression of MOR and related drug research are topics of interest in opioid research, especially the relationship between MOR and tumor recurrence and metastasis. At present, MOR agonists and antagonists have been shown to inhibit cancer cell proliferation and used in combination with tumor molecule-targeting drugs to delay tumor progression[51,56]. KOR and DOR are mainly distributed in the peripheral sensory neurons and spinal cord, and they are involved in analgesia. MOR, KOR, and DOR can be activated by endogenous peptides, such as endorphins, enkephalins, and dynorphins. They could be triggered by other synthetic or semi-synthetic small molecule ligands exogenously[43].

2.2. Pain control

The analgesic effect of morphine is primarily mediated by MOR (Figure 2)[57]. MOR is widely expressed in many pain-related brain regions, including the periaqueductal gray, thalamus, rostral ventromedial medulla, and anterior cingulate cortex, in addition to the spinal cord and primary sensory neurons[58-61]. The mechanisms underlying the analgesic effect are as follows: MOR is activated and then decoupled from the heterotrimeric inhibitory G protein (Gi), which promotes the influx of sodium ion (Na^+) and calcium ion (Ca^{2+}) as well as the inflow of potassium ion (K^+) through cyclic adenosine monophosphate/protein kinase

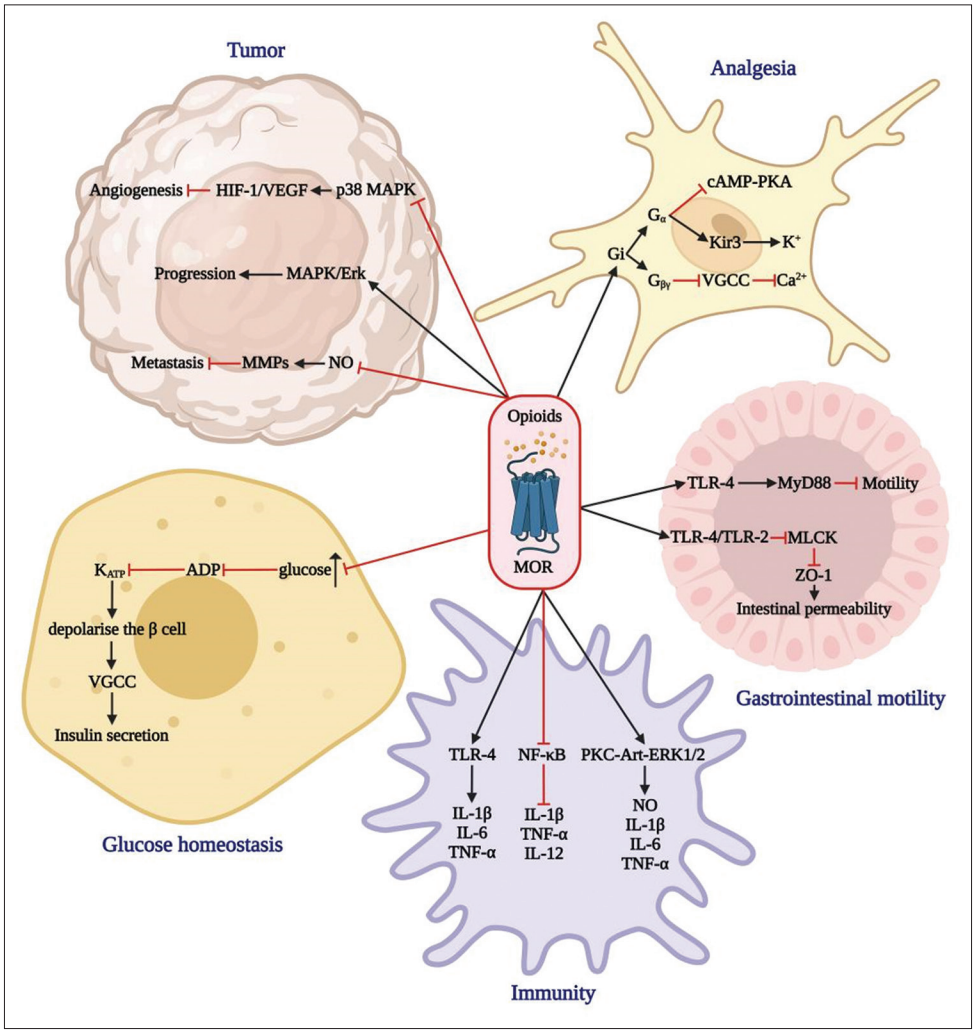

Figure 1. Various biological functions following (MOR) activation. After MOR is activated, it can affect the biological behaviors of tumors, pain inhibition, gastrointestinal motility, blood glucose homeostasis, and immune function through different biological signaling mechanisms. ADP: Adenosine diphosphate; cAMP/PKA: Cyclic adenosine monophosphate/protein kinase A; Gi: Heterotrimeric inhibitory G protein; HIF-1: Hypoxia-inducible factor 1; IL: Interleukin; K_{ATP}: ATP-sensitive potassium channel; Kir3: Inwardly-rectifying potassium channel; MAPK: Mitogen-activated protein kinase; MLCK: Myosin light chain kinase; MMPs: Matrix metalloproteinases; MOR: Mu (μ)-opioid receptor; MyD88: Myeloid differentiation factor-88; NF-κB: Nuclear factor kappa-B; NO: Nitric oxide; TLR-2: Toll-like receptor 2; TLR-4: Toll-like receptor 4; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; VGCC: Voltage-gated calcium channel; ZO-1: Zonula occludens-1. Image created with BioRender.com.

A (cAMP/PKA)[62]. Based on the sensitivity to the selective μ1-opioid receptor antagonist naloxone, MOR is divided into two subtypes, μ1 and μ2. The μ1 subtype is mainly responsible for the analgesic effect of opioids and its effect on body temperature (hypothermia). Upon activation, it produces analgesia at the level above the spinal cord. On the other hand, the μ2 subtype is involved in inhibiting intestinal peristalsis (intestinal obstruction), slowing heart rate and causing respiratory depression after activation, itching, prolactin release, and drug dependence[63].

The previous studies have shown that the MORs expressed in neurons in the dorsal horn of the spinal cord primarily mediate the analgesic effect of morphine in acute pain but are not involved in endogenous opioid analgesia[64]. However, the MORs expressed in excitatory neurons and inhibitory neurons of the spinal cord have the opposite function in pain regulation. Activating MOR in excitatory neurons of the spinal cord leads to analgesic effect, but activating MOR in inhibitory neurons of the spinal cord causes pain sensitivity[65]. At the level of the spinal cord, MOR is expressed in the parabrachial nucleus (a type of nerve nucleus within the pons), which participates in the analgesic effect of morphine in inflammatory pain[61,64,65].

Another study has demonstrated that exogenous and endogenous opioids exert analgesic effect in inflammatory pain by acting on the MORs expressed in glutamatergic and

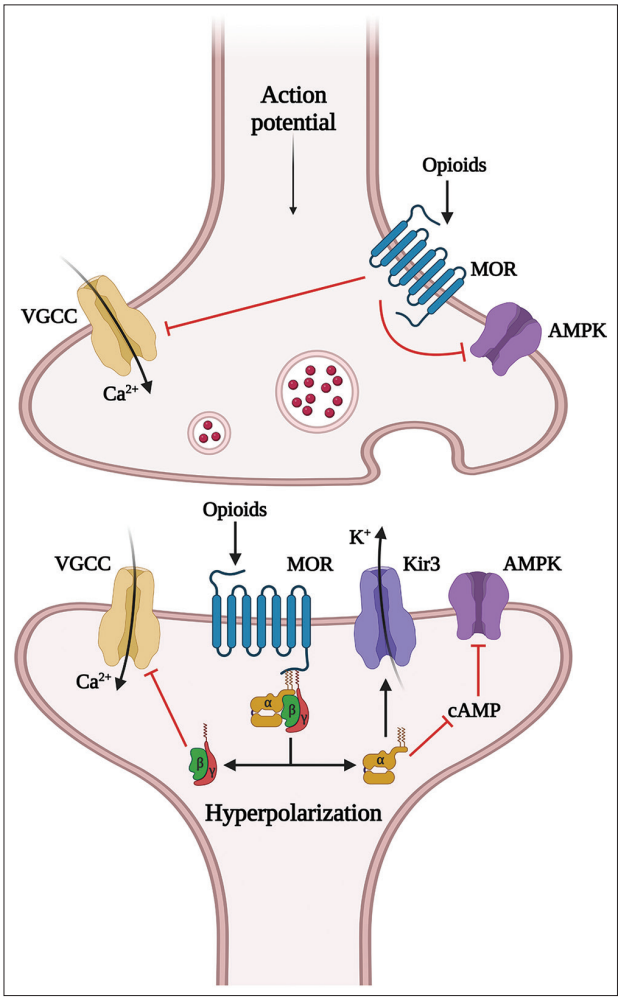

Figure 2. Mechanism of analgesic effect following MOR activation. After the opioid binds to the MOR in the presynaptic membrane, it inhibits voltage-dependent calcium channels, thereby inhibiting the activation of AMPK receptors and the release of vesicles; after binding to the MOR in the postsynaptic membrane, it will decompose Gi into Gα and Gβγ, in which Gα will inhibit the production of cAMP but activate the inward rectification of potassium channel Ki3, promoting the outflow of potassium ions, while Gβγ will flow in with calcium ions at the postsynaptic membrane, which in turn leads to hyperpolarization of the postsynaptic membrane and inhibits the production of pain. AMPK: AMP-activated protein kinase; cAMP: Cyclic adenosine monophosphate; Gi: Heterotrimeric inhibitory G protein; Kir3: Inwardly-rectifying potassium channel; MOR: Mu (μ)-opioid receptor; VGCC: Voltage-gated calcium channel. Image created with BioRender.com

gamma-aminobutyric acid (GABA) neurons, respectively. Exogenous opioids (such as morphine) produce analgesic effect by acting on MOR in glutamatergic excitatory neurons[59,65,66], while endogenous opioids, which are rapidly released in the spinal cord and supraspinal brain regions, inhibit MOR in neurons by acting on GABA to alleviate chronic inflammatory pain[58,67,68]. These studies indicate that both endogenous and exogenous opioids exert analgesic effect through different targets and mechanisms.

2.3. Tumor

MOR can be expressed in many different cancer cells, including BC[69], non-small cell lung cancer (NSCLC)[70], CRC[71], and hepatocellular carcinoma (HCC)[56,72]. In 1989, Scopsi *et al.*[73] was the first to propose that endogenous opioid peptides may be related to cancer progression. Thereafter, many reports have indicated that the activation of MOR may be involved in malignant progression of tumors, which is supported by the evidence that MOR may affect the growth of CRC cells[71] and the prognosis of patients with liver and laryngeal cancer (Figure 3)[55,56]. Therefore, MOR may be used as a new biomarker for tumors and concerned as a new target in cancer treatment.

MOR expression level appears to be associated with cancer prognosis; a high expression promotes cell proliferation, adhesion, migration, and tumorigenesis, while an inhibited expression delays the development of CRC tumors[71]. The μ-opioid receptor gene *OPRM1* is a gene that encodes MOR. The genetic polymorphisms of *OPRM1* (A118G) are associated with tumorigenesis. It has been reported that the G allele of A118G is highly associated with BC in white people, and people with G alleles are three times more likely to be diagnosed with BC. In addition, BC patients with G alleles have lower specific mortality[74]. Compared with the G/G genotype, the A/A genotype has significantly higher risk of esophageal squamous cell carcinoma (ESCC)[75]. Similar studies have shown that the A allele increases the incidence of ESCC in Asians. In addition, evidence has shown that MOR3 is expressed in a variety of cells, such as vascular tissue, and that nitric oxide (NO) is released after morphine action, thus promoting tumor angiogenesis[76,77].

Overall, the bidirectional effect of MOR is evident in tumor development, and many factors, including the number of MOR receptors and drug concentration, lead to the diametrically opposed effects of the receptor in tumor development[71]. Exploring the mechanism of MOR to block its path of promoting tumorigenesis and improve the prognosis of cancer patients will become a promising research direction for the clinical application of opioids and cancer treatment in the future.

3. Relationship between mu-opioid receptor and cancer

Most cancer patients will inevitably experience cancer pain during the disease period. Cancer pain is a type of chronic pain that affects the physical and mental health

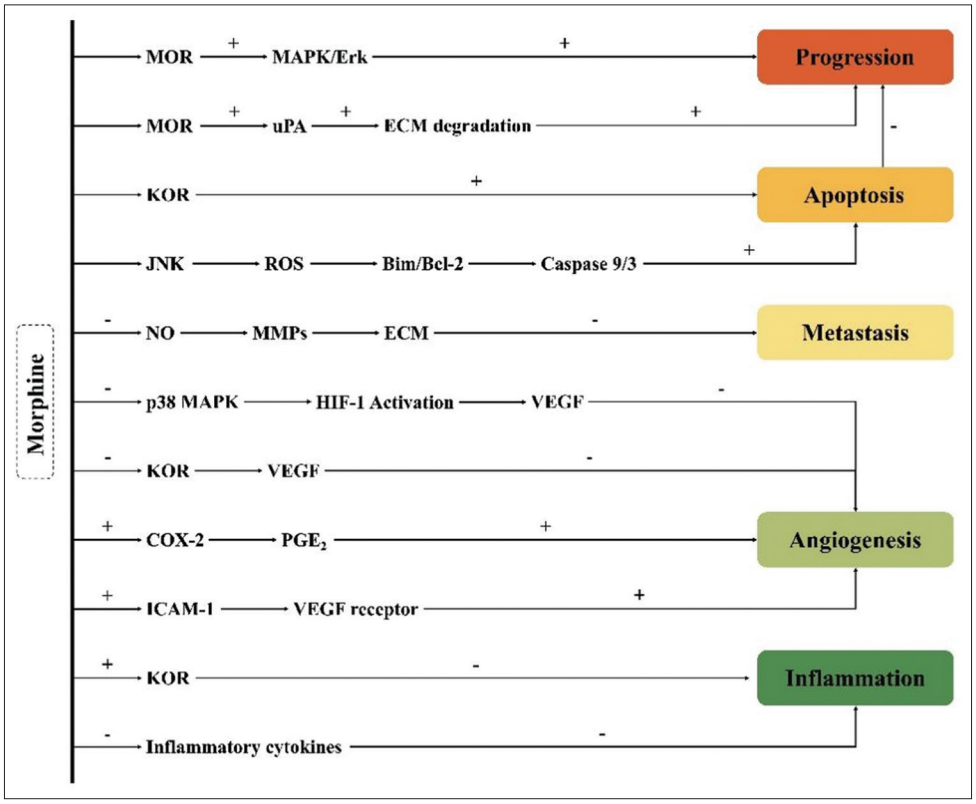

Figure 3. Signaling pathways related to the effect of MOR on tumors. The effect of morphine on receptors can affect tumor progression, apoptosis, metastasis, angiogenesis, and immunity through MAPK/Erk and other pathways. Bcl-2: B-cell lymphoma 2; Bim: Bcl-2 interacting mediator of cell death; COX-2: Cyclooxygenase-2; ECM: Extracellular matrix; HIF-1: Hypoxia-inducible factor 1; ICAM-1: Intercellular adhesion molecule 1; JNK: c-Jun N-terminal kinase; KOR: Kappa (κ)-opioid receptor; MAPK: Mitogen-activated protein kinase; MMPs: Matrix metalloproteinases; MOR: Mu (μ)-opioid receptor; NO: Nitric oxide; PGE_2: Prostaglandin E2; ROS: Reactive oxygen species; uPA: Urokinase plasminogen activator; VEGF: Vascular endothelial growth factor.

of patients and is not conducive to the rehabilitation of cancer patients. An effective control of cancer pain during the perioperative period will significantly improve the prognosis of patients[78]. At present, narcotic analgesics are mostly used in clinical treatment. These drugs can effectively relieve the pain of cancer patients and significantly improve their anxiety[79]. Opioids bind to opioid receptors, giving rise to the effects of MOR activation. The tumor microenvironment plays an important role in tumorigenesis, and there is ample evidence showing the detection of MOR in cancer cells, immune cells, and endothelial cells in the tumor microenvironment in addition to neuronal cells[80]. The binding of endogenous and exogenous opioids to MOR on the cell surface can affect tumor development through a variety of mechanisms, having a dual role (Table 1)[18,47,72]. MOR has attracted the interest of many researchers, and there are now a variety of new immunotherapies related to MOR. MOR may become a novel molecular marker of tumor therapy and a new therapeutic target.

3.1. Tumor proliferation and progression

MOR is expressed in various cancers, such as HCC, CRC, BC, and prostate cancer (PC)[81,82]. Opioid chemicals could affect tumorigenesis and development following MOR activation[83]. Zhang *et al.*[55] demonstrated that high MOR expression may be associated with poor prognosis in patients with lung squamous cell carcinoma (LSCC). Zylla *et al.*[84] found a similar result suggesting that high MOR expression and higher opioids requirement are associated with shorter progression-free survival (PFS) and overall survival (OS) in patients with metastatic PC.

The occurrence and development of cancer are related to the abnormal activation of several intracellular signaling pathways. In NSCLC, the overexpression of MOR increases protein kinase B (AKT) and mammalian target of rapamycin (mTOR) activation, which promotes tumor proliferation[85]. Similarly, Liu *et al.*[86] demonstrated that morphine could promote the growth of H460 cells *in vitro* and *in vivo*, increase Rous sarcoma oncogene cellular homolog (Src) phosphorylation, and activate the

Table 1. Relationship between MOR and different types of cancer

Tumors	Drugs (Opioids)	Effects	Mechanism	Signaling pathway	Result	Conclusion	References
HCC	Morphine	Tumor suppressor				The activation of MOR specifically failed to suppress the malignant phenotype of the tumor	[19]
Pancreatic cancer	Morphine	Tumor promoter	Tumor proliferation, invasion		MOR overexpression increased proliferation in pancreatic cancer cells	MOR was expressed in pancreatic cancer and might be involved in tumor progression and chemoresistance	[118]
Colorectal cancer		Uncertain	Tumor proliferation	cAMP/PKA	There were differences in the expression of MOR in tumor and control tissues	The overall expression of MOR increased in colorectal cancer	[119]
HCC	Xanthomicrol	Tumor promoter	Tumor migration and invasion		Xanthomicrol inhibited the migration and invasion of Huh7 cells	Xanthomicrol is a potential MOR antagonist, with potent anti-migration and anti-invasion ability on Huh7 cells	[55]
Breast cancer		Tumor suppressor	Tumor proliferation	GSK3	Opioid and beta-adrenergic receptors were shown to cross talk through formation of receptor heterodimers to control the growth and proliferation of breast cancer cells	Screening for ligands targeting B2AR and MOR interaction and/or the GSK3 system may help in identifying novel drugs for the prevention of triple-negative breast cancer cell growth and metastasis	[120]
Cervical cancer	Morphine and ketamine	Tumor promoter	Immune function	JAK3/STAT5	The combination of morphine and ketamine might decrease $CD4^+$ percentage, $CD4^+/CD8^+$ ratio, and the levels of cytokines through the JAK3/STAT5 pathway	Morphine-ketamine combination could improve cancer pain and repress immune function via the JAK3/STAT5 pathway in the progression of cervical cancer	[84]
Glioblastoma	Pethidine	Tumor suppressor	Blocks NADH, hinder mitochondrial respiration, enhance the pro-autophagic and pro-apoptotic ceramide levels in cancer cells			Pethidine could inhibit tumor progression	[121]
HCC	mAb	Tumor promoter	Tumor proliferation	CD147/p53 MAPK	Higher expression of MOR in HCC cells than in adjacent tissue	MOR has the potential to be a therapeutic target to treat HCC	[56]
CRC	Morphine and cetuximab	Tumor promoter	Tumor proliferation, migration, invasion, and drug resistance	ERK1/2, AKT-mTOR, RAS-MAPK	Morphine promoted tumorigenesis and cetuximab resistance through activation of EGFR signaling in human CRC	Morphine might be a promising therapeutic target for CRC patients, especially for cetuximab-resistant CRC patients	[122]
NSCLC	Morphine	Tumor promoter	Tumor proliferation, migration, invasion	MOR/Src/mTOR	Morphine enhanced cell migration and invasion	Morphine promoted the malignant biological behavior of H460 cells by activating MOR and Src/mTOR signaling pathways	[123]

(Cont'd....)

Table 1. (*Continued*)

Tumors	Drugs (Opioids)	Effects	Mechanism	Signaling pathway	Result	Conclusion	References
Breast cancer		Tumor promoter	Tumor proliferation, migration, and invasion	Methylation of OPCML promoter	OPCML was downregulated in most breast cancer samples but that this protein was expressed in most adjacent non-tumor samples. The loss or downregulation of OPCML was associated with hypermethylation of its promoter	OPCML exerts tumor-suppressive effect in human breast cancer cells, and the promoter-specific hypermethylation of OPCML plays an important role in human breast cancer development	[124]
HNSCC	No limits	Tumor promoter	Tumor proliferation, migration, and invasion			MOR is implicated in tumorigenesis of HNSCC. MOR could be used as a potential therapeutic target in patients with MOR (+) HNSCC	[108]
CRC	P-137 (a cyclic morphiceptin analog)	Tumor suppressor	Anti-inflammation			The activation of MOR might inhibit CRC progression	[46]
HCC		Tumor promoter	Tumor proliferation and migration	MOR-NFAT	MOR expression was positively related to HCC progression. Silencing MOR greatly reduced HCC-related tumorigenesis both in vitro and *in vivo* and significantly extended the survival of tumor-bearing mice	MOR could be a novel and reliable HCSC marker and a potential therapeutic target against HCC via MOR-NFAT signaling	[125]
HCC		Tumor promoter			High MOR expression in HCC tumors was correlated with poor prognosis. MOR inhibitors suppressed cell growth, invasion, and metastasis *in vitro* and in subcutaneous and orthotopic xenograft models	MOR has an oncogenic function in hepatocarcinogenesis, and MOR inhibitors might be a promising strategy for HCC therapy	[126]
Breast cancer	Morphine	Tumor promoter	Tumor angiogenesis	MAPK, PKB/AKT	–	Clinical use of morphine could potentially be harmful in patients with angiogenesis-dependent cancers	[127]
Breast cancer	Morphine	Tumor suppressor			Morphine significantly reduced the cell vitality, growth, and colony formation rate of MCF-7	Morphine might be unable to promote the progression of cancer in breast cancer patients receiving morphine analgesia	[128]
Breast cancer	Morphine	Tumor promoter	Tumor angiogenesis	MAPK/ERK, PI3k/AKT, VEGF	–	Morphine promotes angiogenesis and promotes breast cancer progression	[47]
LLC	Morphine	Tumor suppressor	Tumor angiogenesis	HIF-1α/p38 MAPK	–	Morphine, in addition to its analgesic function, can be exploited for its antiangiogenic potential	[129]

(Cont'd....)

Table 1. (*Continued*)

Tumors	Drugs (Opioids)	Effects	Mechanism	Signaling pathway	Result	Conclusion	References
NSCLC		Tumor promoter	Tumor angiogenesis	VEGF	MOR expression increased significantly in cancer samples from patients with lung cancer compared with adjacent control tissue	The expression level of MOR might be associated with tumor progression	[130]
Melanoma		Tumor promoter	Immune function		There was a positive correlation between the expression of β-endorphin and tumor progression in melanoma tissues	μ-opioid peptides might play a major role in cancer progression by modulating immune response. This finding might have implications for future optimization of immune-interventions for cancer	[89]
HCC		Tumor promoter	Tumor progression	MAPK	The downregulation of MOR inhibited both *in vivo* and in vitro human liver cancer progression	Blocking MOR has potential in cancer therapy	[88]
NSCLC		Tumor promoter	Tumor progression	AKT-mTOR	MOR overexpression increased AKT and mTOR activation, proliferation, and extravasation in human bronchioloalveolar carcinoma cells	The exploration of MOR in NSCLC merits further study both as a diagnostic and therapeutic option	[131]

AKT: Protein kinase B; B2AR: Beta-2 adrenergic receptor; cAMP/PKA: cyclic adenosine monophosphate/protein kinase A; CRC: Colorectal carcinoma; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; GSK3: Glycogen synthase kinase 3; HCC: Hepatocellular carcinoma; HIF-1α: Hypoxia-inducible factor 1 alpha; HNSCC: Head and neck squamous cell carcinoma; JAK3/STAT5: Janus kinase 3/signal transducer and activator of transcription 5; LLC: Lewis lung carcinoma cells; mAb: monoclonal antibody; MAPK: Mitogen-activated protein kinase; MOR: Mu (μ)-opioid receptor; mTOR: Mammalian target of rapamycin; NADH: Nicotinamide adenine dinucleotide; NFAT: Nuclear factor of activated T-cells; NSCLC: Non-small cell lung cancer; OPCML: Opioid-binding protein/cell adhesion molecule; PI3k: Phosphoinositide 3 kinase; Src: Rous sarcoma oncogene cellular homolog; VEGF: Vascular endothelial growth factor

phosphoinositide 3 kinase (PI3k)/AKT/mTOR pathway, which can further promote the malignant biological behavior of H460 cells (Figure 4). Lu *et al.*[87] found that the downregulation of MOR was able to inhibit human LC progression both *in vivo* and *in vitro* and detected the activation of mitogen-activated protein kinase (MAPK)-related signaling pathways while conducting a clinical study of patients with LC. Similar results have been reported by Zhang *et al.*[56] who found that the expression of MOR in HCC cells and tissue was higher than in non-tumor cells or adjacent tissue and the specific anti-MOR monoclonal antibody (mAb) 3A5C7 inhibited the proliferation of HepG2 and Huh7 cells through the MOR-CD147-p53-MAPK pathway (Figure 5).

The association between MOR expression and tumorigenesis has been reported in many other types of cancer. In CRC cells, there were differences in the expression of MOR in tumor and control tissues and in the activation of cAMP/PKA signaling pathway, suggesting a higher expression of MOR in colorectal cancer[88]. Moreover, MOR overexpression has shown to increase PC cell proliferation and may be involved in tumor progression and chemoresistance[89].

Opioids usually exert their corresponding effects by agonizing MOR. The different and even opposite effects of opioids in various cancers may be due to factors such as cell type, drug, and dose. Overall, the above reports have shown that in different types of tumor cell, the expression of MOR is closely related to the occurrence and development of tumors. MOR is anticipated to be used as a novel biomarker and therapeutic target for some cancers, necessitating further exploration and research on cancer immunotherapy.

3.2. Tumor angiogenesis

Angiogenesis is an essential process for tumorigenesis, tumor growth, and metastasis, and it is regulated by various factors. At present, there is a growing interest in the close relationship between MOR and tumorigenesis and its influence on tumor angiogenesis. As solid tumors grow, tumor cells move further away from their vascular supply. The hypoxic tension or hypoxia subsequently stimulates tumor cells to secrete

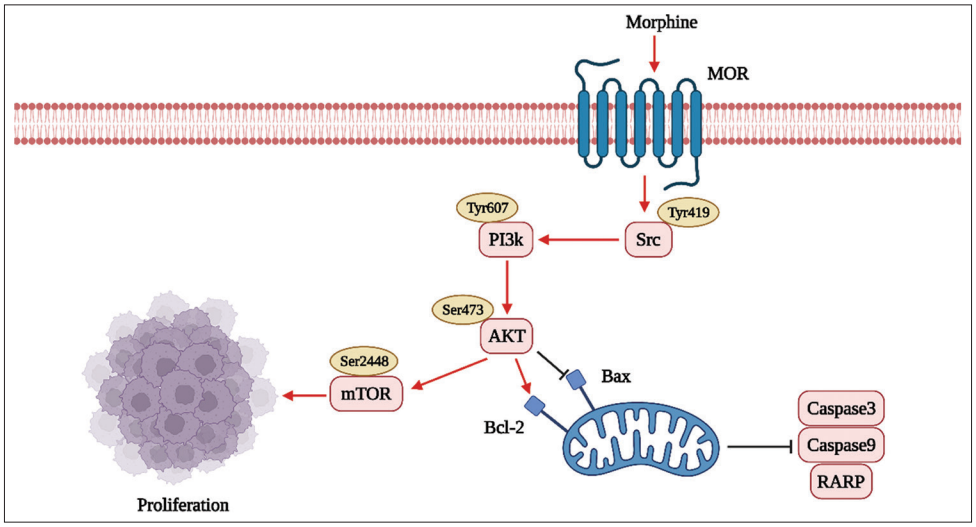

Figure 4. Possible mechanisms by which morphine promotes tumor progression and metastasis after activating MOR. Morphine combined with MOR can activate the Src/PI3k/AKT/mTOR signaling pathway, thereby promoting tumor proliferation, while inhibiting the expression of Bax and inhibiting tumor apoptosis. AKT: Protein kinase B; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; MOR: Mu (μ)-opioid receptor; mTOR: Mammalian target of rapamycin; PI3k: Phosphoinositide 3 kinase; Src: Rous sarcoma oncogene cellular homolog. Image created with BioRender.com.

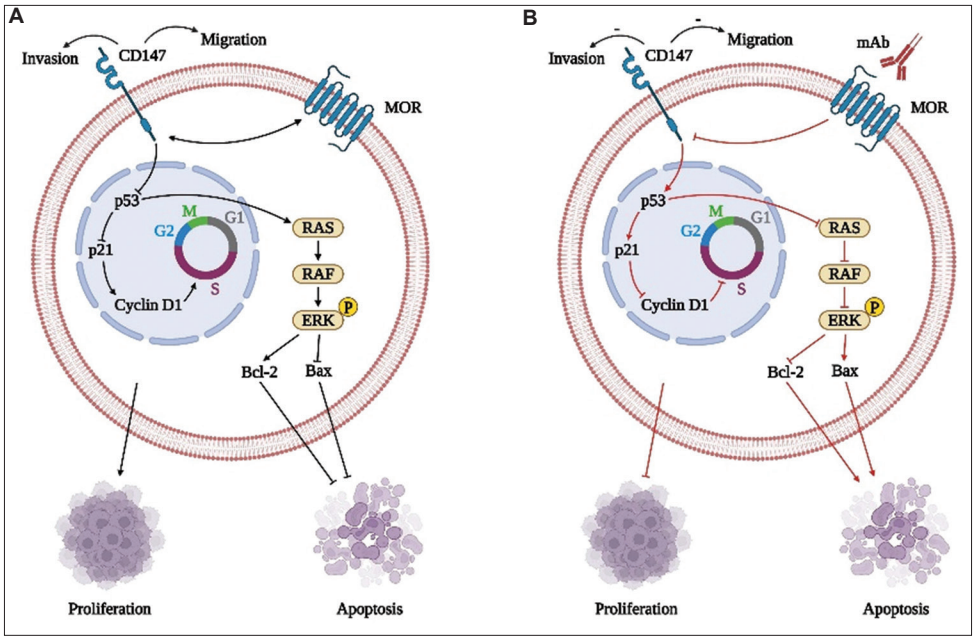

Figure 5. (A) MOR and CD147 interact to promote tumor progression. The interaction between MOR and CD147 inhibits the expression of p53/p21 but activates the MAKP and RAS/RAF/ERK pathways, thereby promoting the expression of Bcl-2 and inhibiting tumor apoptosis. (B) MOR mAb inhibits the progression of cancer cells. The combination of MOR and mAb results in increased p53/p21 production and an inhibition of MAPK pathway activation, which can inhibit tumor proliferation, while Bax expression increases, promoting tumor apoptosis. Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; ERK: Extracellular signal-regulated kinase; mAb: Monoclonal antibody; MOR: Mu (μ)-opioid receptor. Image created with BioRender.com.

angiogenic factors[90]. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor secreted by hypoxic tumor cells within a developing tumor mass that initiates endothelial cell germination, migration, and proliferation[91], while hypoxia-inducible factor (HIF) regulates the adaptive response of tumor cells to hypoxia, which activates genes, such as *VEGF*, and the transcription of VEGF receptor genes through binding of hypoxia response element (HRE) in the gene promoter region, thereby promoting the production of blood vessels within solid tumors.

The *in vitro* use of morphine in the treatment of Lewis lung carcinoma cells (LLC) has been demonstrated to inhibit the nuclear translocation of HIF-1α and post-translational modification/phosphorylation of HIF-1α by inhibiting the hypoxia-induced mitochondrial p38 MAPK pathway, thus reducing the transcription and secretion of VEGF[92]. Therefore, angiogenesis in LCC could be inhibited by blocking the HIF-1α/p38 MAPK pathway following MOR activation. Interestingly, Singleton *et al.*[93] found contrary results showing a significantly higher expression of MOR in lung cancer samples than in adjacent control tissues and that the effect of MOR on tumorigenesis might be due to increased VEGF expression (Figure 6). Similar results have been observed in a study of breast cancer patients, whereby morphine induced metastasis formation by upregulation of urokinase plasminogen activator (uPA) expression and induced angiogenesis and tumor progression by transactivation of VEGF receptor[94].

NO plays a very important role in tumor angiogenesis[95]. Research results have suggested that morphine can reduce mitochondrial membrane potential by binding to MOR on vascular endothelial cells, promoting the production of NO, stimulating the expression of pro-apoptotic factors Bak and Bax, thereby activating caspase-3 and caspase-7, and ultimately inducing the apoptosis of vascular endothelial cells as well as inhibiting the production of blood vessels[96]. Interestingly, another study has shown that the activation of MOR on the surface of vascular endothelial cells could induce the production of NO[97] by increasing intracellular calcium concentration, which can promote the proliferation and migration of vascular endothelial cells and increase their permeability. NO participates in tumor angiogenesis by endothelial constitutive NO synthetase (ec-NOS) activation, cyclic guanosine monophosphate (cGMP) elevation, MAPK activation, and fibroblast growth factor 2 (FGF-2) expression (Figure 7)[98].

Therefore, by exploring the effect of MOR activation on tumor angiogenesis, it may be possible to use MOR as the target to achieve the purpose of treating tumors by activating/inhibiting angiogenesis of certain cancer cells.

3.3. Tumor immunity

The tumor microenvironment (TME) plays a very important role in the occurrence and development of cancer[99,100]. In the tumor microenvironment, activated inflammatory cells release multiple inflammatory mediators and molecules, such as interleukin-2 (IL-2), IL-6, and tumor necrosis factor alpha (TNF-α), transforming the tumor microenvironment into an environment that is more suitable for cancer cell survival[101]. Opioids have a dual

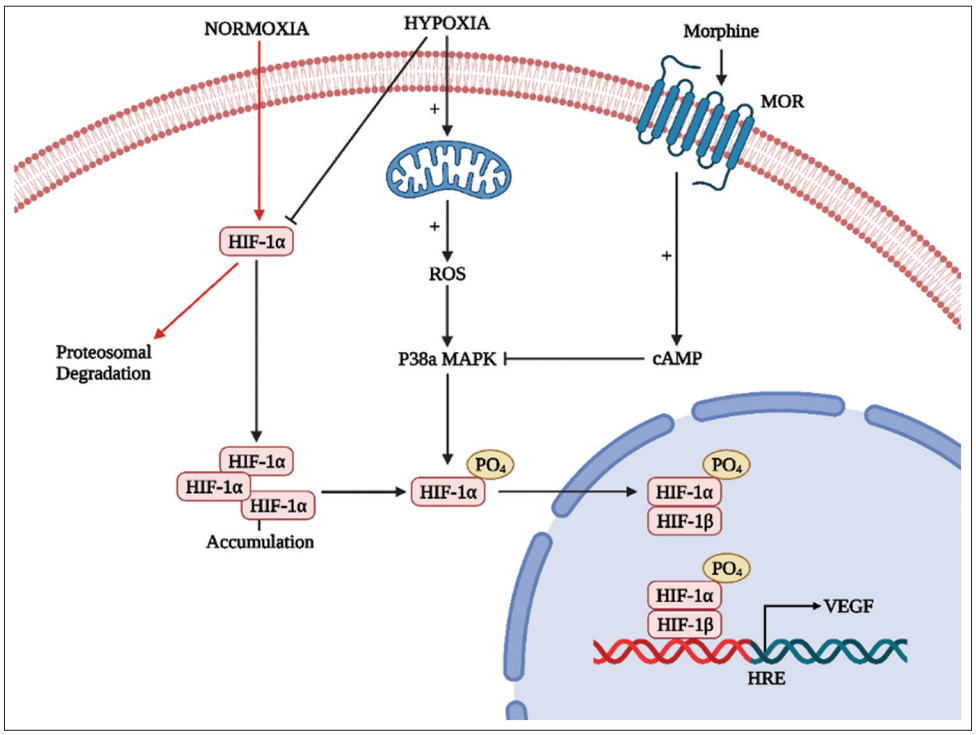

Figure 6. A model of possible mechanisms affecting tumor angiogenesis after MOR activation. The treatment of morphine activates MOR, reduces hypoxia, induces p38 MAPK, and thus HIF-1α activation. cAMP: Cyclic adenosine monophosphate; HIF-1α: Hypoxia-inducible factor 1 alpha; HRE: Hypoxia response element; MAPK: Mitogen-activated protein kinase; MOR: Mu (μ)-opioid receptor; ROS: Reactive oxygen species; VEGF: Vascular endothelial growth factor. Image created with BioRender.com.

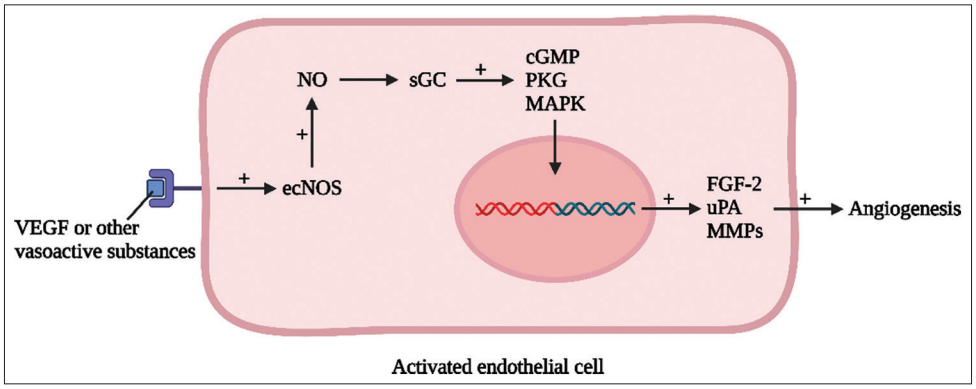

Figure 7. A model of the mechanism by which endogenous NO affects tumor angiogenesis. The binding of VEGF or other vasoactive substances to receptors on the cell membrane can promote the production of endogenous NO, which in turn promotes the production of cGMP and the activation of PKG/MAPK, thereby promoting the expression of uPA and affecting tumor angiogenesis. cGMP: Cyclic guanosine monophosphate; ec-NOS: Endothelial constitutive NO synthetase; FGF-2: Fibroblast growth factor 2; MAPK: Mitogen-activated protein kinase; MMPs: Matrix metalloproteinases; NO: Nitric oxide; PKG: Protein kinase G; sGC: Soluble guanylyl cyclase; uPA: Urokinase plasminogen activator; VEGF: Vascular endothelial growth factor. Image created with BioRender.com.

role in regulating inflammation and tumors: inhibiting inflammatory response and tumor growth and allowing tumors to escape attacks from the immune system[102]. Koodie *et al.*[103] suggested that morphine could change the cell adhesion molecules on white blood cells and endothelial cells in LCC by activating MOR, thereby inhibiting the migration and recruitment of white blood cells to reduce angiogenesis and tumor growth. Jiang *et al.*[104] isolated T cells from peripheral blood mononuclear cells (PMBCs) using anti-CD3 magnetic beads in patients with cervical cancer (CC); the *in vitro* experiment demonstrated that the combination of morphine and ketamine may suppress immune function in CC progression by reducing $CD4^+$ percentage, $CD4^+/CD8^+$ ratio, and the levels of interferon gamma (IFNγ), IL-2, and IL-17 through the Janus kinase 3/signal transducer and activator of transcription 5 (JAK3/STAT5) pathway.

Zielinska *et al.*[105] used P-317, a cyclic analog of morphiceptin, to stimulate opioid receptors to induce an anti-inflammatory response. In a colitis-associated CRC model, a significant difference in colorectal tumor development was observed between vehicle- and P-317-treated mice. P-317 reduced TNF-α expression and inflammatory responses in mice as well as the total number of colorectal tumors[105]. Boehncke *et al.*[106] showed that μ-opioid peptides may play a major role in melanoma progression by activating MOR and modulating immune response.

Based on the studies on the effect of MOR activation on tumor immunity, we speculate that the signaling pathway associated with immune response following MOR activation may serve as a new target for the treatment of certain cancers.

3.4. Cancer therapy

As one of the drugs commonly used in cancer patients, opioids, in addition to analgesic effect, have multifaceted impact on the occurrence and development of tumors[107]. Many recent tumor immunotherapies are associated with MOR[102]. Methylnaltrexone (MNTX), an antagonist of MOR, has been widely used in clinical trials to improve survival in patients with advanced cancer[46]. Gorur *et al.*[108] demonstrated that MNTX strongly inhibited the proliferation, invasion, and migration of FaDu and MDA686Tu cells (head and neck squamous cell carcinoma cell lines) but had no effect on UMSCC47 cells (one cell line). Similarly, Singleton *et al.*[109] showed that the infusion of peripheral MOR antagonist MNTX significantly attenuated tumor growth. Therefore, MOR may be a promising potential target for chemotherapeutic agents.

Recently, tumor immunotherapy has been extensively studied, and its applications in clinical practice has expanded[110]. For example, antibodies against the immune checkpoint programmed cell death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) have been approved for the treatment of certain types of cancer, such as NSCLC, bladder cancer, HCC, and melanoma, and have demonstrated improved efficacy[111,112]. However, the role of PD-1 signaling in neurons remains unclear. Chen *et al.*[113] observed attenuated morphine-induced analgesia in PD-1-knockout mice and decreased morphine action through the inhibition of PD-1 effect by nivolumab injection. In dorsal root ganglion (DRG) neurons, PD-1 and MOR receptors are co-expressed. When PD-1 is knocked down, the inhibitory effect of morphine on calcium channels is attenuated. In the spinal dorsal horn, morphine

inhibits the release of excitatory neurotransmitters from the presynaptic membrane and the postsynaptic membrane depolarization, both of which are attenuated by PD-1 inhibition[111]. Therefore, further exploration of the interaction between PD-1 and MOR is needed to modify the immunotherapy regimen and develop new immunotherapies for different types of cancer.

To date, the effect of morphine on cancer progression has been extensively studied. However, recent studies have suggested that exogenous opioids can also regulate the proliferation of cancer cells by binding to opioid growth factor receptor (OGFR)[114,115]. OGFR differs from classical opioid receptors in that it does not have any analgesic effect and is a negative regulator of cell proliferation. Research findings have shown that lung cancer cells express OGFR and morphine might inhibit the progression of lung cancer by interacting with OGFR[116]. On this basis, we speculate that a combination therapy targeting MOR and OGFR may be beneficial for inhibiting cancer progression. In short, immunotherapy for cancer treatment is of great research value, and further research on MOR may provide new ideas for cancer treatment.

4. Conclusion and perspective

Recent investigation has demonstrated that high MOR expression could promote the proliferation of cancer cells by activating AKT/mTOR, cAMP/PKA, and MAPK-related signaling pathways, which would directly lead to poor prognosis in LSCC patients, shortened PFS and OS in patients with metastatic PC, proliferation of PC cells, and increased chemotherapy resistance. However, downregulating the expression of MOR could inhibit the progression of human liver cancer. On the other hand, MOR activation could inhibit angiogenesis and tumor development in LCC by inhibiting the HIF-1α/p38 MAPK pathway. These findings partially indicate that there may be a "dual action" relationship between opioids and the MOR on which opioids mainly act and the development of cancer. Therefore, further exploration of the specific mechanism and inhibition of the signaling pathway that can promote tumorigenesis and development are the research directions on the impact of tumor duality using MOR.

Several factors, including cancer type, cancer process, time of drug administration, drug concentration, and drug administration route, have more or less influence on the role of opioids in the development of cancer. A large number of studies have demonstrated some controversial results due to the use of opioids at different concentration levels, thus activating different subtypes of MOR and resulting in the dual effect on cancer progression and prognosis. MOR agonists have shown to promote the development of cancer cells at therapeutic concentrations by activating MOR1 and MOR3 as well as inhibit cancer cell proliferation at high concentrations. However, there are studies that have revealed contradicting results, such as a study of renal cell carcinoma demonstrating that morphine has little effect on tumor proliferation at low concentrations but has significant proliferative effect at high concentrations[117]. These results indicate that MOR drug concentration variations produce noticeable outcomes that are closely related to cancer types and gene expression, and the related effect can be blocked by MOR inhibitors. These findings have revealed the potential of MOR as a new target in cancer treatment. However, the molecular mechanism of such possible influencing factors is unclear, and there is a lack of relevant case records in clinical practice. Therefore, there is a need to design more prospective studies to determine the relationship between the overall survival rate of cancer patients and opioid use (such as duration of administration and drug concentration), the level of MOR expression in different cancer cells, and the changes in MOR expression in different cancer processes. Through clinical epiphenomena, we can steer the research direction of molecular mechanism and understand the role of MOR in inhibiting cancer development, thus blocking its path of promoting tumorigenesis and tumor development as well as improving the prognosis of cancer patients.

In conclusion, based on the previous research results, we anticipate the possibility of further exploring the interactions among MOR, PD-1, OGFR, *etc*., and using these relationships to study new immunotherapies for cancer treatment and provide novel ideas for the treatment of tumors.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

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Consent for publication

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